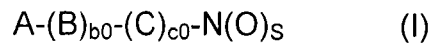


07/21/2008

I. **AMENDMENTS TO THE CLAIMS:**

1. (Currently Amended) A method of ~~preventing or reducing the degenerative effects on~~ degeneration of the cartilaginous matrix comprising administering to a subject with arthritis an effective amount of one or more compounds or salts thereof having the following formula:



wherein:

s is an integer and is equal to 1 or 2;

c0 is an integer and is equal to 0 or 1;

b0 is an integer and is 0 or 1; with the proviso that at least one of c0 and b0 is different from zero;

A = R-T₁-, wherein

R- is the radical of a non steroidal antiinflammatory precursor drug excluding the compounds having 2-oxo-1H-indolic structure, or the radical of a non steroidal antiinflammatory/analgesic drug;

T₁ = (CO)_t or (X)_{t'}, wherein X = -O-, -S-, -N(R_{1C})-, R_{1C} is H or C₁-C₅ linear or branched alkyl, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -T_B-X₂-T_{BI}- wherein

T_B and T_{BI} are equal or different;

$T_B = (\text{CO})$ when the reactive function in the precursor drug is $-\text{OH}$ or $-\text{NH}(\text{R}_{1\text{C}})$; $T_B = \text{X}$, as above, when the reactive function in the precursor drug is $-\text{COOH}$;

$T_{\text{BI}} = (\text{CO})_{\text{tx}}$ or $(\text{X})_{\text{txx}}$, wherein tx and txx have the value of 0 or 1; with the proviso that $\text{tx} = 1$ when $\text{txx} = 0$, $\text{tx} = 0$ when $\text{txx} = 1$; X is as above;

X_2 is a bivalent linking group as defined below;

C is the bivalent radical $-\text{T}_\text{C}-\text{Y}-$ wherein

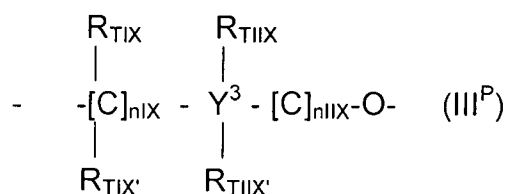
when $b_0 = c_0 = 1$: $T_\text{C} = (\text{CO})$ when $\text{tx} = 0$, $T_\text{C} = \text{X}$ when $\text{txx} = 0$, X being as above;

when $b_0 = 0$: $T_\text{C} = (\text{CO})$ when $t = 0$, $T_\text{C} = \text{X}$ when $t' = 0$, X being as above;

when $c_0 = 0$: $\text{tx} = 0$, $T_{\text{BI}} = \text{X} = -\text{O}-$;

Y is:

Y_p :



wherein:

nIX is an integer from 0 to 10;

nIIX is an integer from 1 to 10;

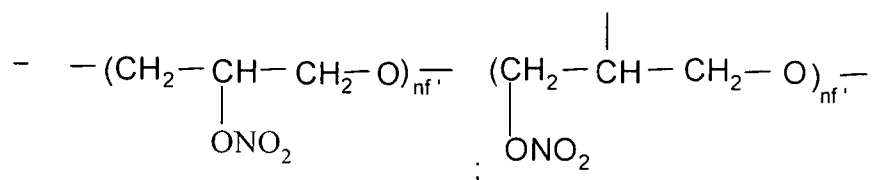
R_{TIX} , $\text{R}_{\text{TIX}'}$, R_{TIIX} , $\text{R}_{\text{TIIX}'}$, equal to or different from each other are H or $\text{C}_1\text{-C}_4$ linear or branched alkyl;

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring containing one or two nitrogen atoms having 5 or 6 atoms,

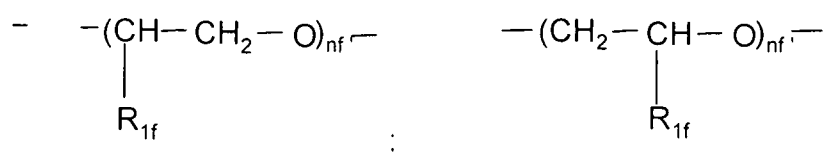
or Y can be:

Y_0 , selected from the following:

- a $-R'O-$ alkylenoxy group wherein R' is linear or branched when possible C_1-C_{20} , or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above; or one of the following groups:

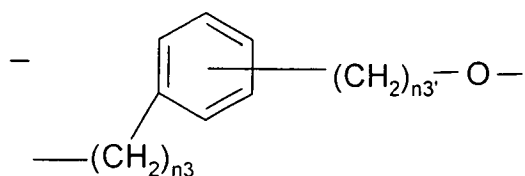


wherein n_f' is an integer from 1 to 6;



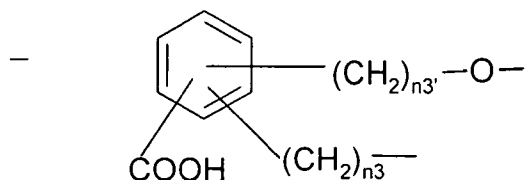
wherein $R_{1f} = H, CH_3$ and n_f' is an integer from 1 to 6;

or Y is Y_{Ar} and is selected from the following:



wherein n_3 is an integer from 0 to 3 and n_3' is an integer from 1 to

3;



wherein n3 and n3' have the above meaning;

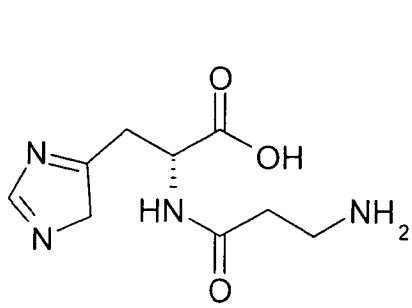
X₂, bivalent radical is such that the corresponding precursor of B, -T_B-X₂-T_{BI}- wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with -N(Z^I)(Z^{II}), wherein Z = H or C₁-C₁₀ linear or branched alkyl, Z^I, Z^{II} equal or different have the Z values as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor of B is selected from the following:

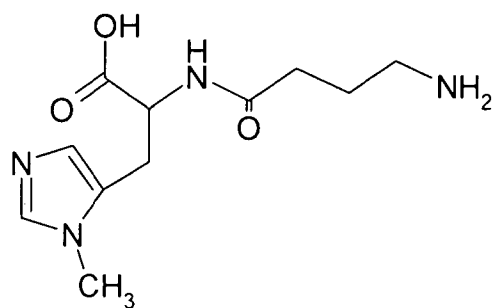
- aminoacids,
- hydroxyacids,
- aromatic and heterocyclic mono- and polyalchols,
- compounds containing at least one free acid function.

2. (Withdrawn) The method of claim 1, wherein the precursor of B is selected from the following:

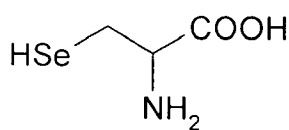
- aminoacids selected from the following: L-carnosine (formula CI), anserine (CII), selenocysteine (CIII), selenomethionine (CIV), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII), glutathione (CIX) or esters thereof



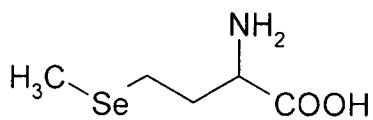
(CI)



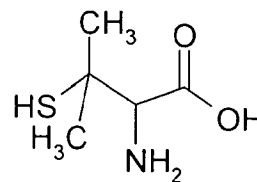
(CII)



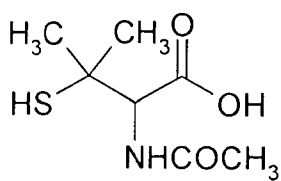
(CIII)



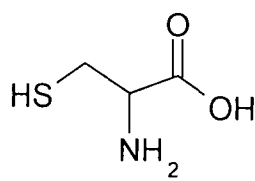
(CIV)



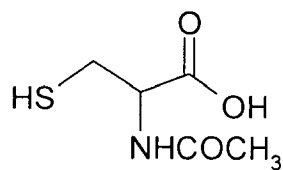
(CV)



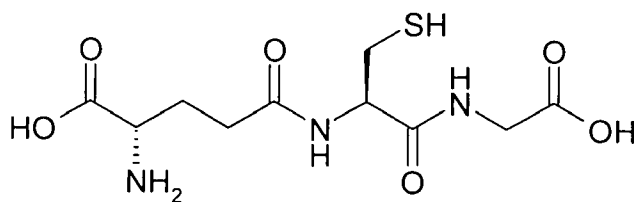
(CVI)



(CVII)

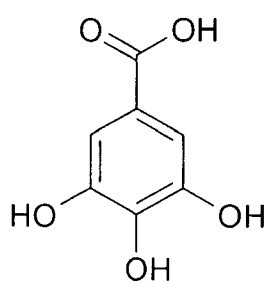


(CVIII)

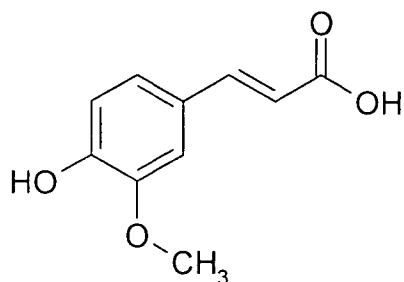


(CIX)

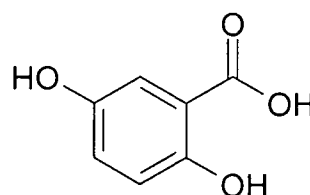
- hydroxyacids, selected from the following: gallic acid (formula DI), ferulic acid (DII), gentisic acid (DIII), citric acid (DIV), caffeic acid (DV), dihydrocaffeic acid (DVI), p-cumaric acid (DVII), vanillic acid (DVIII):



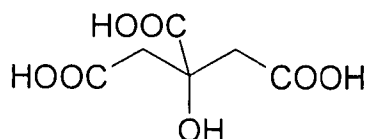
(DI)



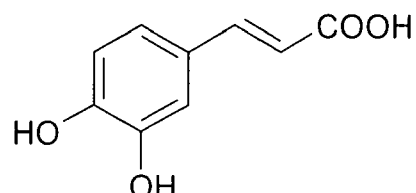
(DII)



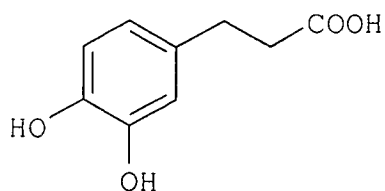
(DIII)



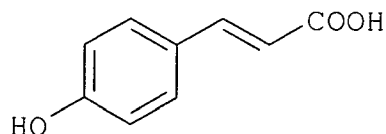
(DIV)



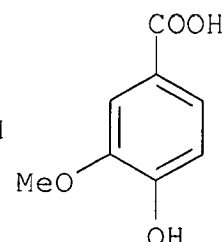
(DV)



(DVI)

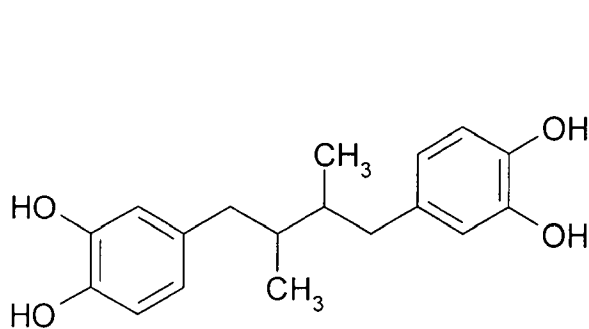


(DVII)

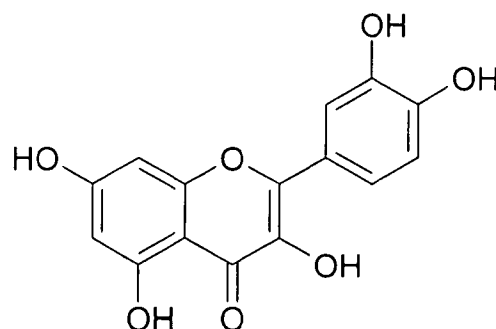


(DVIII)

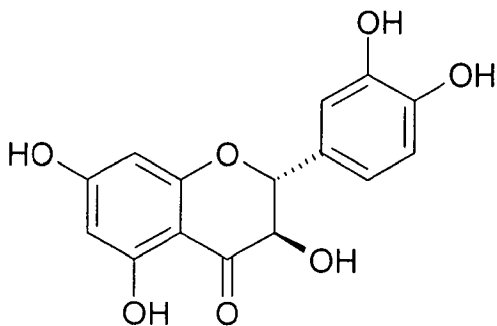
- aromatic and heterocyclic mono- and polyalcohols, selected from the following: nordihydroguaiaretic acid (EI), quercetin (EII), catekin (EIII), kaempferol (EIV), sulphurethyne (EV), hydroquinone (EVIII), gossypol (EIX), reductic acid (EX), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), propyl gallate (EXIII), 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate (EXXIV), allopurinol (EXXXI); saccharose (EC), ascorbic (ECI) and isoascorbic acid (ECII), p-cumaric alcohol (ECIII), 4-hydroxy-phenylethylalcohol (ECIV), coniferyl alcohol (ECV):



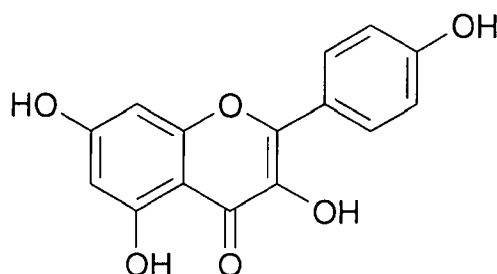
(EI)



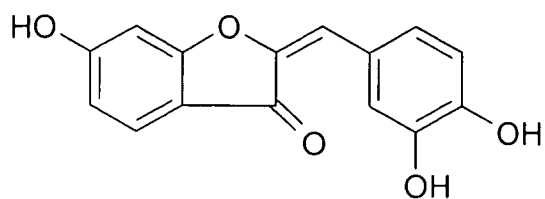
(EII)



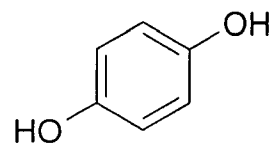
(EIII)



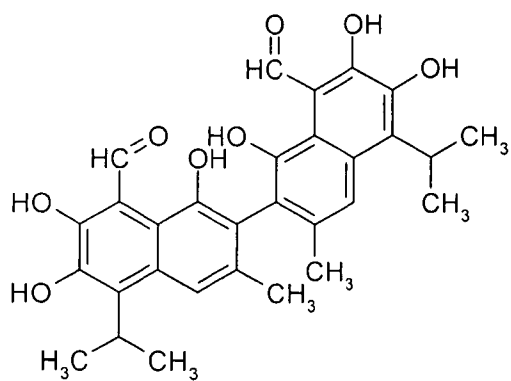
(EIV)



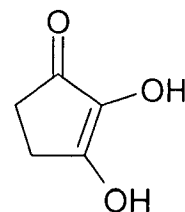
(EV)



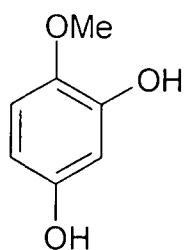
(EVIII)



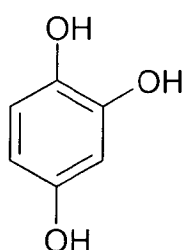
(EIX)



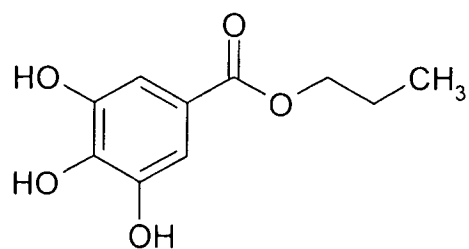
(EX)



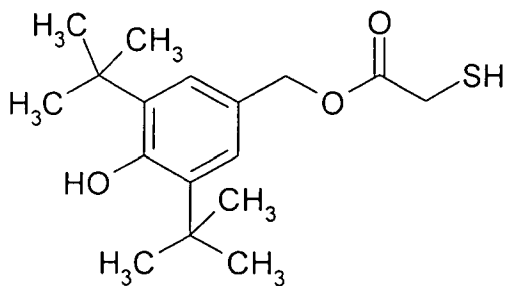
(EXI)



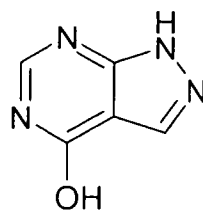
(EXII)



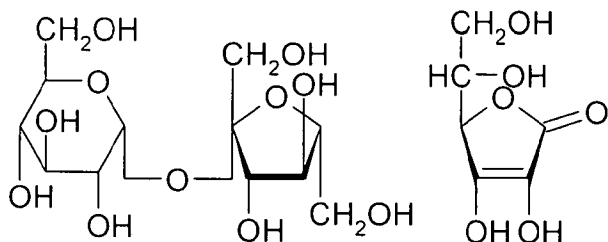
(EXIII)



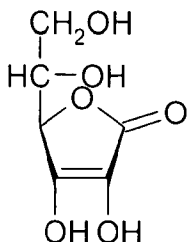
(EXXIV)



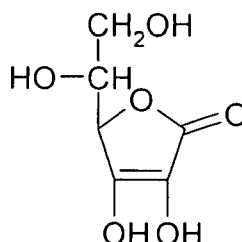
(EXXXI)



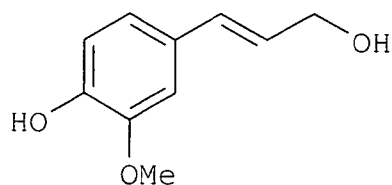
(EC)



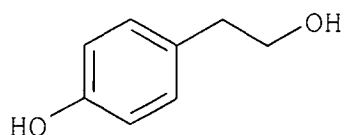
(ECI)



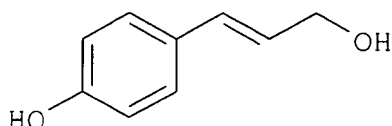
(ECII)



(ECIII)

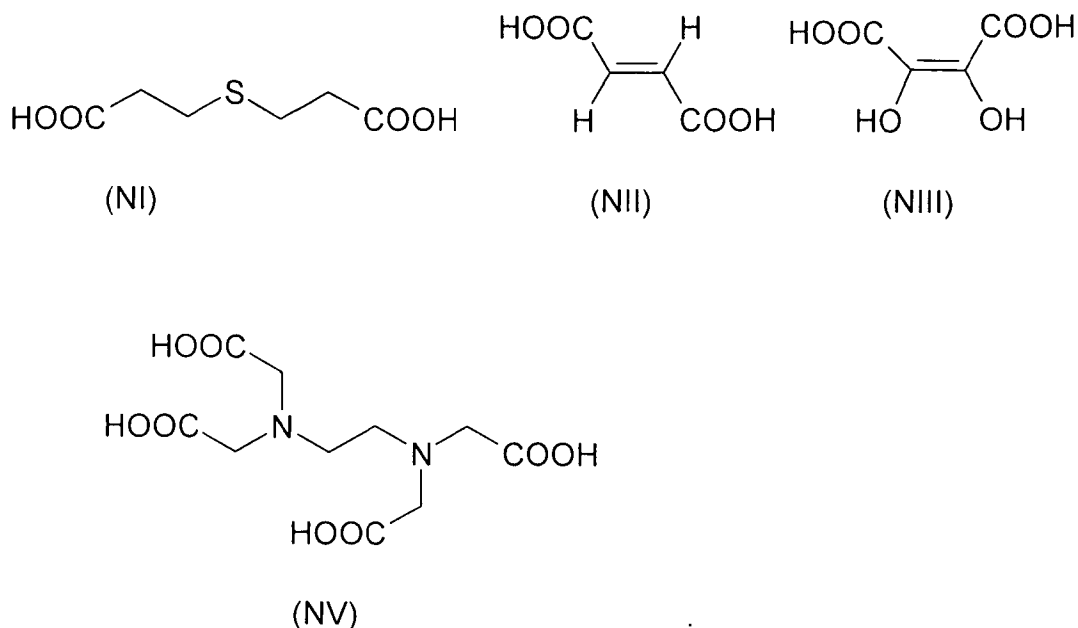


(ECIV)



(ECV)

- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid (NI), fumaric acid (NII), dihydroxymaleic acid (NIII), edetic acid (NV):

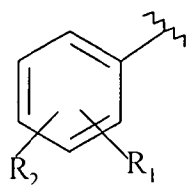


3. (Previously Presented) The method of claim 1, wherein in the compounds of formula (I):
 - when $b_0 = c_0 = 1$, the bonds between the drug radical and X_2 and between X_2 and Y are, independently the one from the other, of ester, thioester, amide type;
 - when $b_0 = 0$ and $c_0 = 1$ the bond between the drug radical and Y is of ester, thioester, amide type.

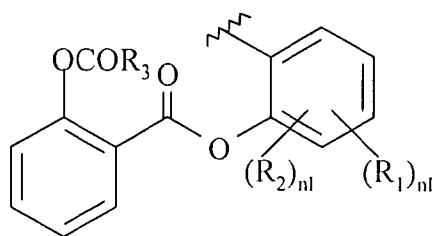
4. (Currently Amended) The method of claim 1, wherein the R radical is selected from the following groups:

Group I)

la)



lb)



wherein:

R_1 is H or $-OCOR_3$; wherein R_3 is methyl, ethyl or C_3 - C_5 linear or branched alkyl, or the residue of an heterocycle with only one ring having 5 or 6 atoms partially or totally hydrogenated, or aromatic, containing one or more heteroatoms

independently selected from O, N and S;

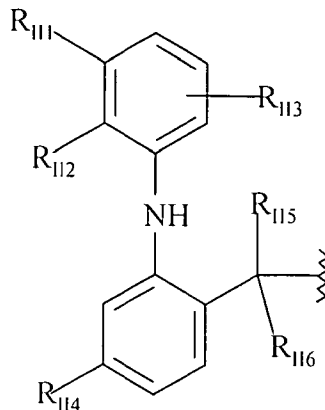
R_2 is hydrogen, hydroxy, halogen, C_1 - C_4 linear or branched alkyl, C_1 - C_4 linear or branched alkoxy; a C_1 - C_4 linear or branched perfluoroalkyl ~~perfluoroalkyl~~; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

with the proviso that in formula Ia) R_1 and R_2 are not contemporaneously H;

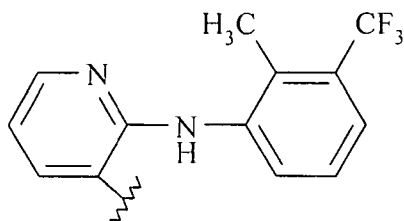
in formula lb) nl is an integer 0 or 1;

Group II)

Ila)



IIb)



wherein:

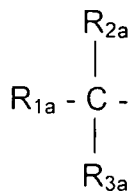
R_{II5} is H, C₁-C₃ linear or branched alkyl;

R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it is benzyl;

R_{II1}, R_{II2} and R_{II3} are independently hydrogen, C₁-C₆ linear or branched alkyl, or C₁-C₆ linear or branched alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

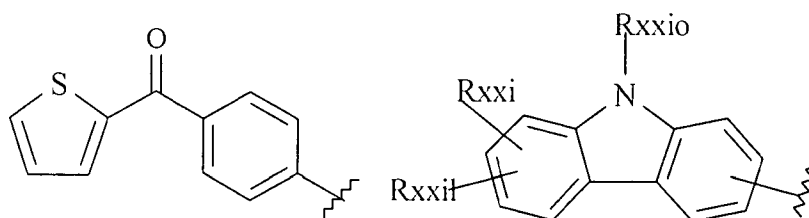
IIb) is the residue of the 2-[(2-methyl-3-(trifluoro methyl)phenyl)amino]-3-pyridincarboxylic acid when T₁ = -CO- and the free valence is saturated with OH the compound is known as flunixin;



wherein:

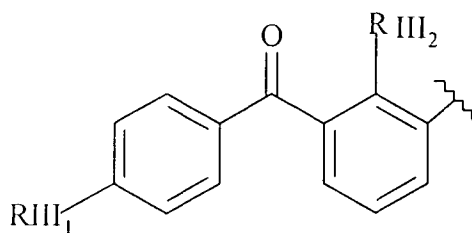
R_{2a} and R_{3a} are H, C_1 - C_{12} linear or branched, substituted or not, alkyl or allyl, with the proviso that when one of the two is allyl the other is H;

R_{1a} is selected from:

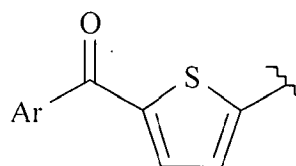


(II)

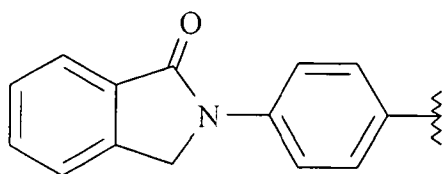
(XXI)



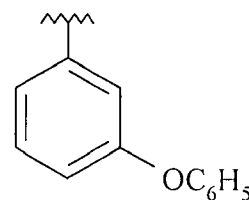
(IV)



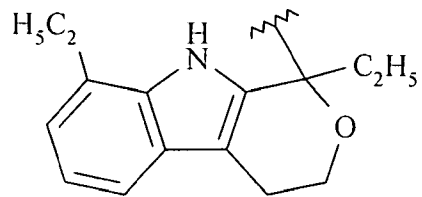
(XXXV)



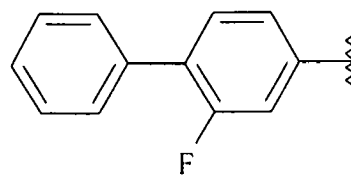
(VI)



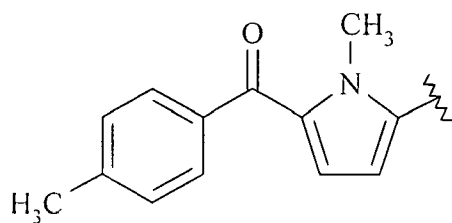
(VII)



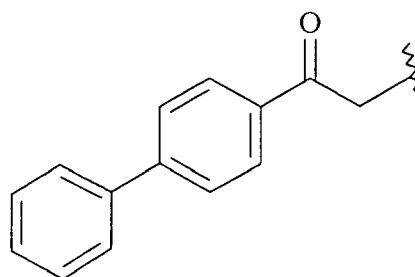
(VIII)



(IX)

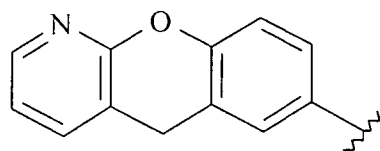


(X)

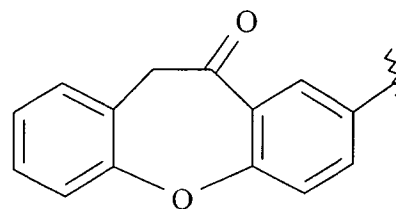


(III)

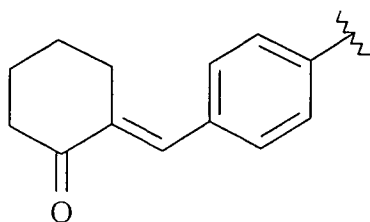
IIID) R_{1a} corresponds to the following formulas:



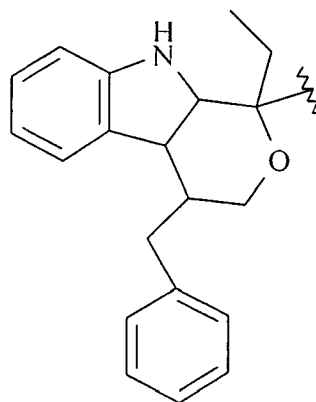
(IIIa)



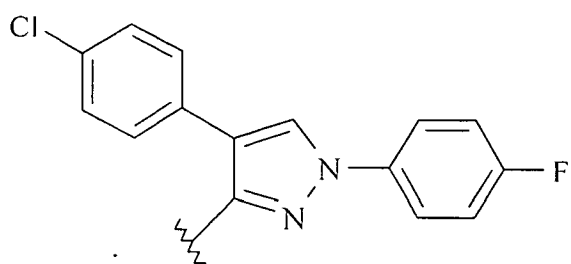
(XXX)



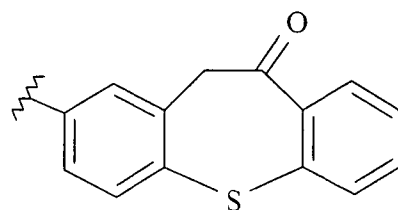
(XXXI)



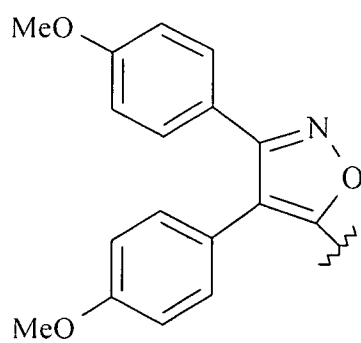
(XXXII)



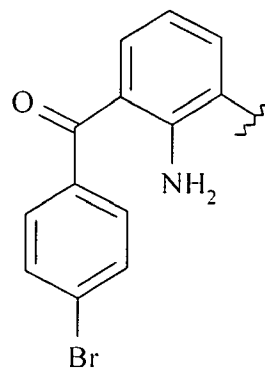
(XXXIII)



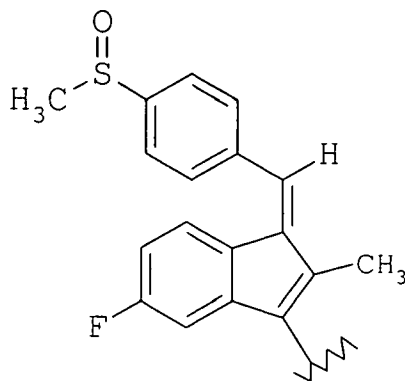
(XXXVI)



(XXXVII)



(XII)



(XXXX)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue:
 R_{III1} is H, SR_{III3} wherein R_{III3} is C_1 - C_4 linear or branched alkyl;
 R_{III2} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue:
 R_{xxio} is H, alkyl from 1 to 6 C atoms linear or branched, C_1 - C_6
 alkoxy carbonyl linked to a C_1 - C_6 alkyl, C_1 - C_6 carboxyalkyl, C_1 - C_6 alkanoyl,
 optionally substituted with halogens, benzyl or halobenzyl, benzoyl or
 halobenzoyl;
 R_{xxi} is H, halogen, hydroxy, CN, C_1 - C_6 alkyl containing or not containing
 OH groups, C_1 - C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} wherein R_{xxi2} is C_1 - C_6
 alkyl; C_1 - C_3 perfluoroalkyl; C_1 - C_6 carboxyalkyl containing or not containing
 OH groups, NO_2 , amino; sulphamoyl, di-alkyl sulphamoyl with C_1 - C_6 alkyl,
 or difluoroalkylsulphonyl with C_1 - C_3 alkyl;

R_{xxi1} is halogen, CN, C₁-C₆ alkyl containing one or more OH groups, C₁-C₆ alkoxy, acetyl, acetamido, benzyloxy, SR_{III3} being R_{III3} as above, C₁-C₃ perfluoroalkyl, hydroxy, C₁-C₆ carboxyalkyl, NO₂, amino, C₁-C₆ mono- or di-alkyl-amino; sulphamoyl, C₁-C₆ di-alkyl-sulphamoyl, or di-fluoroalkylsulphamoyl as above; or R_{xxi} together with R_{xxi1} is a C₁-C₆ alkylene-dioxy;

- when R_{1a} is as defined in formula (XXXV) tiaprofenic acid residue:
Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, alkanoyl and C₁-C₆ alkoxy, C₁-C₆ trialkyl, cyclohexyl, cycloheptyl, heteroaryl, furyl containing or not containing OH, pyridyl;
- when R_{1a} is as defined in formula (II), suprofen residue, R_{3a} is H, R_{2a} is methyl and T₁ = -CO-;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when T₁ = -CO-, R_{2a} = H and R_{3a} = CH₃; of indobufen when R_{2a} is equal to H and R_{3a} = C₂H₅; T₁ = -CO-;
- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when R_{2a} = R_{3a} = H and T₁ = -CO-;
- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when R_{3a} = H, R_{2a} = CH₃ and T₁ = -CO-;
- when R_{1a} is as defined in formula (III), R is the fenbufen residue when R_{2a} = R_{3a} = H and T₁ = -CO-;

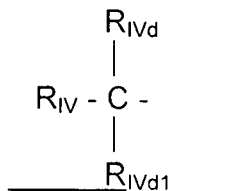
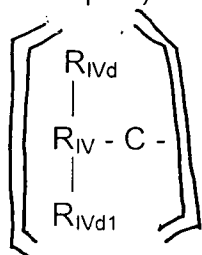
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$, $T_1 = -CO-$;
- when R_{1a} is as defined in formula (X) R is the tolmetin residue when $R_{2a} = R_{3a} = H$, $T_1 = -CO-$.

In group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$ the pranoprofen residue is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid;
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$ the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid;
- (XXXII), when $R_{2a} = R_{3a} = H$, the pemedolac residue is obtained; when $R_{2a} = R_{3a} = H$ $T_1 = -CO-$;
- (XXXIII), when $R_{2a} = R_{3a} = H$, the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazol acid derivatives;
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$ the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or aminic group, or with the carboxylic function the compounds are known as dibenzotiepin derivatives;
- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid when the residue is CH_2-COOH ;
- (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

- (XXXX) when $R_{2a} = R_{3a} = H$ the sulindac residue is obtained: (Z)-5-fluoro-2-methyl-1-[[4-(methyl sulphonyl) -phenyl]methylene]-1H-inden-3-acetic acid;

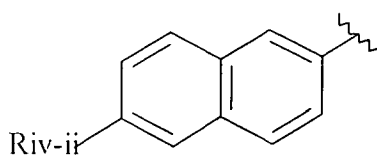
in Group IV) R is



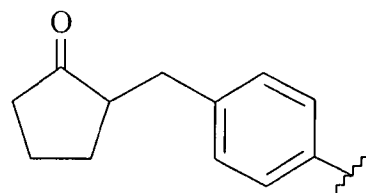
wherein:

R_{IVd} and R_{IVd1} are at least one H and the other an alkyl from C_1 to C_6 linear or branched, or difluoroalkyl with C_1 - C_6 alkyl, or R_{IVd} and R_{IVd1} form together a methylene group;

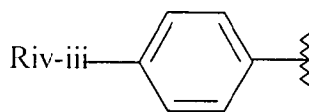
R_{IV} has the following meaning;



(IIB)



(XB)



(IIIB)

wherein the compounds of group IV) have the following meanings:

- in formula (IIB):

R_{IV-ii} is C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_7 alkoxyethyl, C_1 - C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1 - C_6 alkoxy, difluoroalkoxy with C_1 - C_7 alkyl, C_1 - C_7 alkoxyethyl, alkylthiomethoxy with C_1 - C_7 alkyl, alkyl methylthio with C_1 - C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with the C_1 - C_8 alkyl; $T_1 = -CO-$;

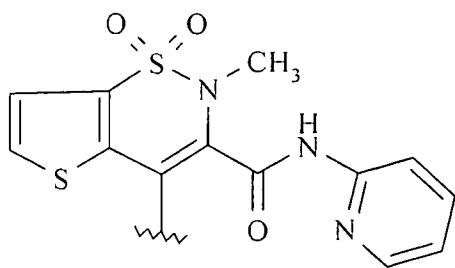
- in formula (XB), of which the loxoprofen residue has been indicated, the compounds wherein R_{IVd} is H and R_{IVd1} is CH_3 ;

- in formula (IIIB):

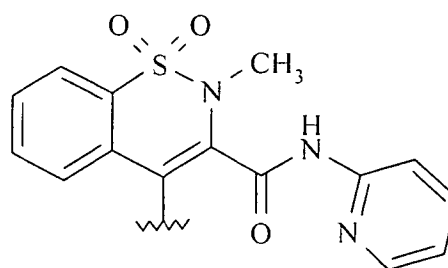
R_{IV-iii} is a C_2 - C_5 branched or not branched alkyl, C_2 and C_3 alkoxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 C atoms, optionally substituted in position 1 by a C_1 - C_2 alkyl;

and $R_{IVd} = H$, R_{IVd1} is CH_3 , compound known as ibuprofen residue, $T_1 = -CO-$;

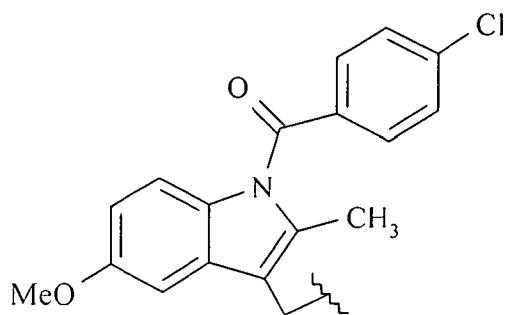
Group V)



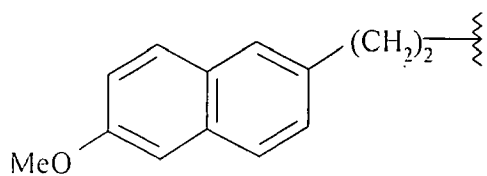
(VIIC)



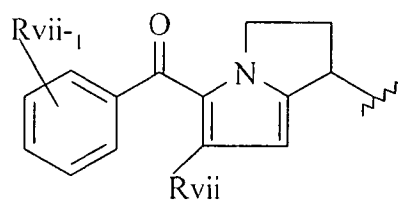
(IXC)



(IVC)

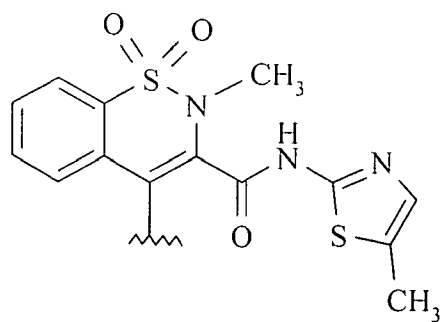


(IIIC)

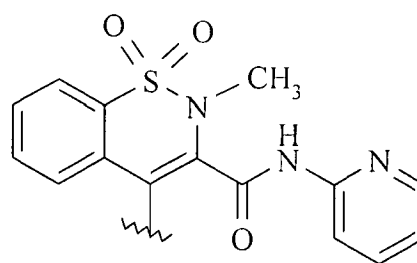


(IIC)

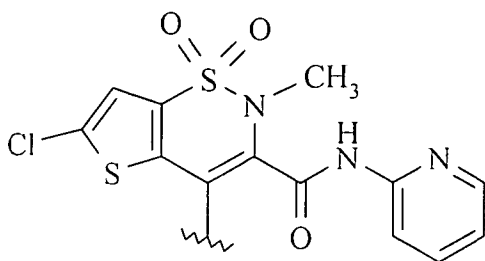
Group VE)



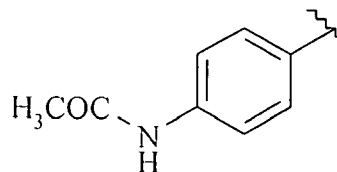
(XC)



(XI)



(XIII)



(XXXXV)

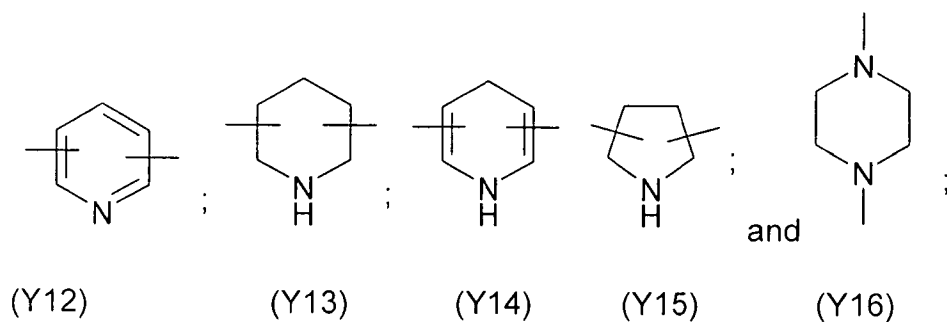
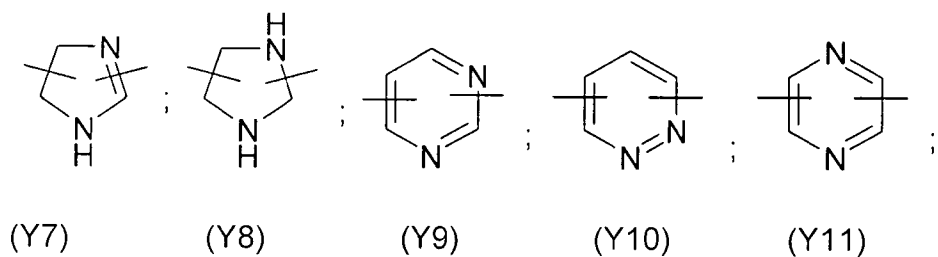
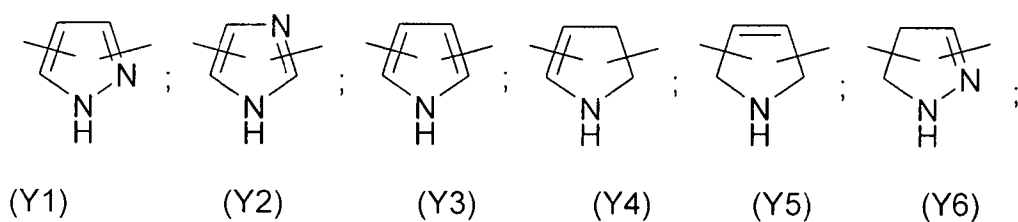
In group V), the compounds have the following meanings:

- when R is the formula (IIC),
 R_{VII} is H or a C_1 - C_4 linear or branched alkyl;
 R_{VII-1} is R_{VII} , or C_1 - C_4 linear or branched alkoxy; Cl, F, Br; the position of R_{VII-1} being ortho, or meta, or para;
- when R is the formula (VIIC),
of which the tenoxicam residue has been indicated, $T_1 = -O-$;
- when R is the formula (IXC),
wherein $T_1 = -O-$, the piroxicam residue has been indicated;
- when R is the formula (IIIC),
wherein $T_1 = -CO-$, of which the nabumetone residue has been indicated;
- when R is the formula (IVC),
wherein $T_1 = -CO-$, of which the indomethacin residue has been indicated;
- when R is the formula (XC), the residue X is known as meloxicam;
- when R is the formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$;
- when R is the formula (XIII) and the valence is saturated with H, the

residue derives from lornoxicam;

- when R is the formula (XXXXV), $T_1 = -O-$ and the valence is saturated with H, the compound known as paracetamol is obtained.

5. (Withdrawn) The method of claim 1, wherein in the compounds of formula (I) Y^3 of formula (III^P) of C is selected from the following bivalent radicals:



6. (Withdrawn) The method of claim 5, wherein Y^3 is selected from the following:
- (Y12) with the two free valences in the ortho positions with respect to the nitrogen

atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol)
3,5-disubstituted.

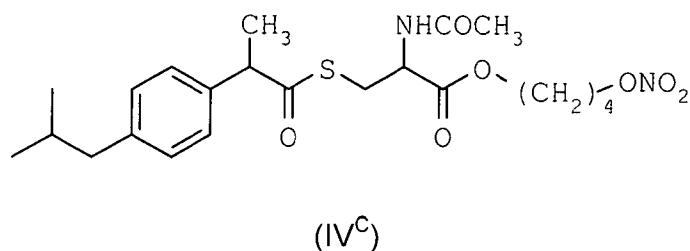
7. (Previously Presented) The method of claim 1, wherein the compounds or salts thereof of formula (I) are selected from the group consisting of:

2-acetyloxybenzoic acid 3-nitrooxymethyl phenyl ester (I^C);

2-fluoro- α -methyl[1,1'-biphenyl]-4-acetic acid 4-nitrooxy butylester (II^C);

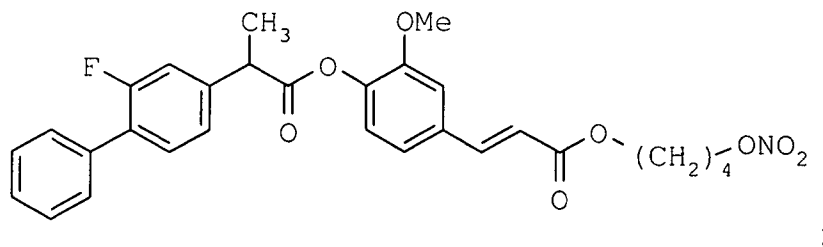
2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-nitrooxy butyl ester (III^C);

(S)-N-acetyl-[α -methyl-4-(2-methylpropyl)benzen-acetyl] cysteine 4-nitrooxybutylester having formula:



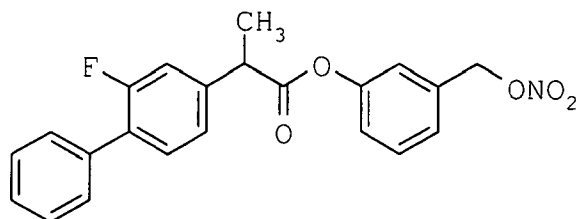
4-nitrooxybutanoic acid 4-acetylaminophenylester (V^C);

trans-3-[4-[2-fluoro- α -methyl(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy) butyl ester, having formula:



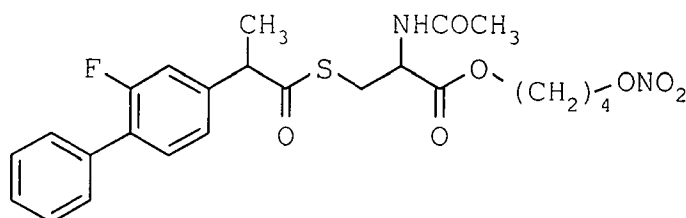
(VI^C)

2-Fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 3-(nitrooxymethyl)phenyl ester
having formula:



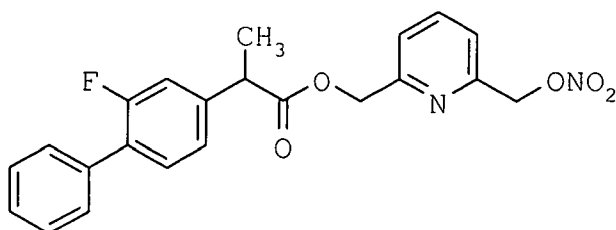
(VII^C)

(S)-N-acetyl-[2-fluoro-alpha-methyl(1,1'-biphenyl)-4-acetyl] cysteine 4-(nitrooxy)butyl ester having formula:



(VIII^C)

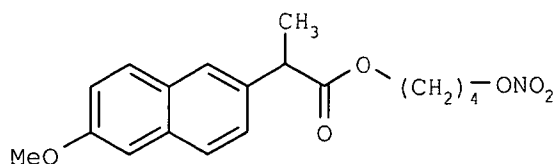
2-Fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 6-(nitrooxy methyl)-2-methylpyridyl ester having formula



(XI^C)

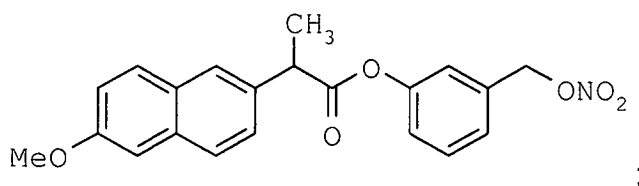
(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 4-(nitrooxy)butyl ester

having formula :



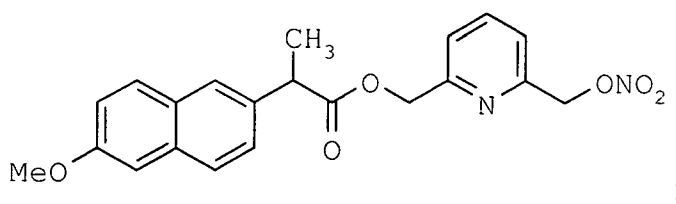
(X^c);

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 3-(nitrooxymethyl)phenyl ester having formula:



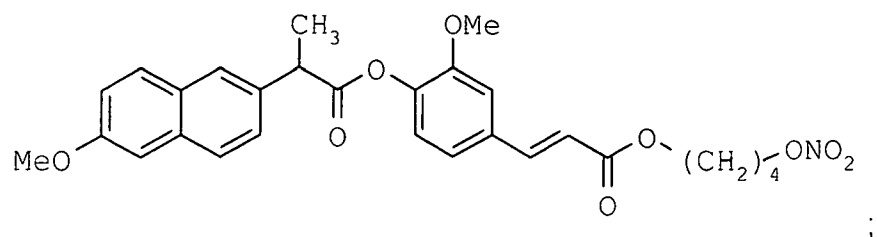
(XI^b)

(S)-6-methoxy-alpha-methyl-2-naphthalenacetic acid 6-(nitrooxymethyl)-2-methylpyridyl ester having formula:



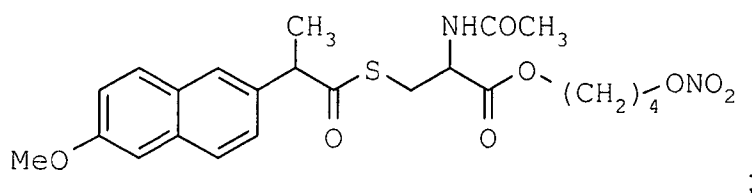
(XI^c)

trans-3-[4-[6-methoxy-alpha-methyl-2-naphthalenacetyl oxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy)butyl ester having formula:



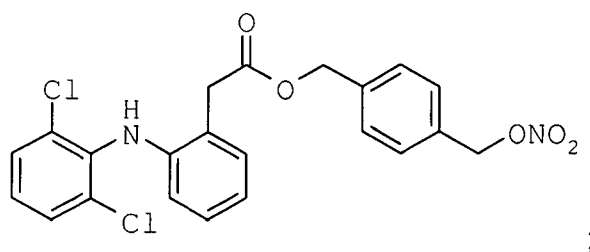
(XIII^c)

(S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthaleneacetyl) cysteine 4-(nitrooxy)butyl ester having formula:



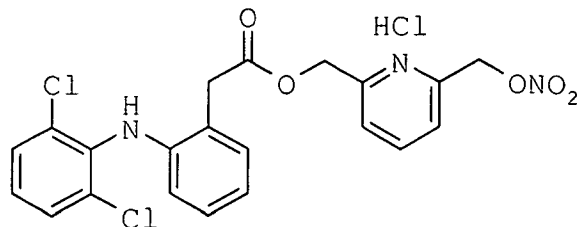
(XIV^c)

2-[(2,6-dichlorophenyl)amino]benzenacetic acid 4-(nitrooxy methyl)phenylmethyl ester having formula:



(XV^c)

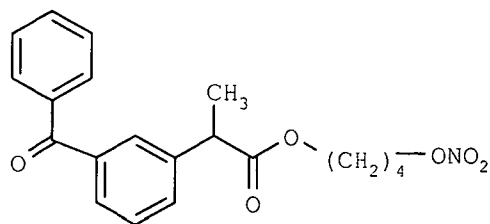
2-[(2,6-dichlorophenyl)amino]benzenacetic acid 6-(nitrooxymethyl)-2-methylpyridyl hydrochloride ester having formula:



;

(XVI^c)

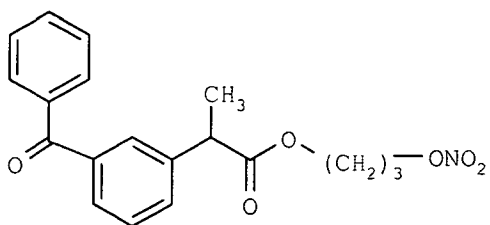
(S)-3-benzoyl-alpha-methyl-benzenacetic acid 4-(nitro oxybutyl) ester having formula:



;

(XVII^c)

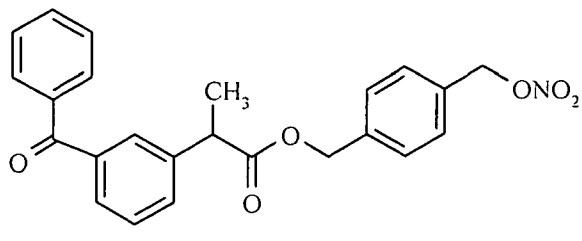
(S)-3-benzoyl-alpha-methyl-benzenacetic acid 3-(nitro oxypropyl) ester having formula:



;

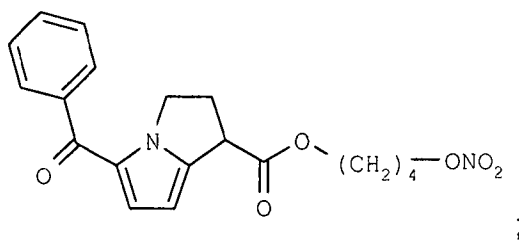
(XVIII^c)

(S)-3-benzoyl-alpha-methyl-benzenacetic 4-(nitro oxymethyl) phenylmethyl ester having formula:



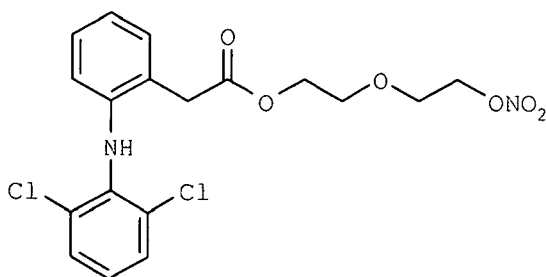
(XIX^c)

5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid 4-(nitrooxy)butyl ester
having formula:



(XXI^c)

2-[(2,6-dichlorophenyl)amino]benzenecetic acid 5 (nitro oxy)ethyloxyethyl ester
having formula:



(XX^c)

1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid 3-(nitrooxymethyl)phenyl ester (XXI^c).

8. (Previously Presented) The method of claim 1, wherein the compounds or salts thereof of formula (I) are administered by oral, parenteral or topical administration.
9. (Currently Amended) The method of claim 1, wherein relapses of ~~degenerative effects on degeneration of the~~ cartilaginous matrix in subjects with arthritis are reduced prevented.